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When a Simple Serum Ferritin Level Measurement Misleads the Diagnosis of a Neonate in the NICU: A Case Report and Review of Literature

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ABSTRACT

This case report describes a newborn girl born with non-immune hydrops fetalis with bicytopenia and elevated iron indexes. A genetic study which was done revealed a positive result for the H63D homozygous mutation. Iron overload is rare in patients homozygous for the H63D mutation because of its variable penetrance, especially in the neonatal period. The possibility of neonatal hemochromatosis (NH) on top of positive results for hereditary hemochromatosis (HH) was anticipated. Despite all the recommended healthcare measurements being provided for both diagnoses, the child developed liver failure of unspecified etiology and was deceased afterward.

Keywords: HFE gene, p.H63D, Ferritin, iron overload, neonate, non-immune hydrops fetalis, anemia, Thrombocytopenia.

INTRODUCTION

Hereditary hemochromatosis (HH) is an autosomal recessive disease that leads to excessive absorption of iron and its deposition in different organs tissues, eventually causing organ damage in advanced ages [(1-3,6)]. High Ferritin (HFE)-related HH is the most common genetic defect in the northern European population. It has been estimated that it affects 1 case in 200-500 individuals in the US [(2,4,5)]. C282Y and H63D are the two mutations in HFE gene most commonly identified [(1,6)]. Being the most penetrant [(4)], C282Y has been well established in the development of the disease and the overall clinical significance. H63D penetrance, on the other hand, was found to be variable and less likely to be associated with an overt significance of HH [(1,6)].

On the other hand, hemochromatosis in neonates (NH) is a rarely found disorder. Iron accumulation in liver and other organs is an anticipated outcome in most of the cases. Originally, it was thought to be HH, however, recent hypotheses came to conclude that >95% of cases had been described were attributed to a gestational alloimmune disorder (GALD). Non-GALD etiologies can rarely cause NH.

In this case report, we describe a newborn girl who was born hydropic with bicytopenia. All investigations were insignificant, except for hyperferritinemia and the genetic panel which were positive for the H63D homozygous mutation. The importance of basic lab investigations and consideration of all the possible diagnoses, including rare ones, will be emphasized in this case report.

The study was done after approval of ethical board of Imam Abdulrahman Bin Faisal university

CASE SCENARIO

This full-term newborn girl is a product of normal vaginal delivery, born to a 34-year-old mother, originally from Northern Saudi Arabia, with no antenatal care. The mother gave birth to 3 normal siblings. The parents are non-consanguineous, and both are healthy. Her Apgar scores were 1 and 5 at 1 and 5 minutes respectively. Her birth weight was 2.9 kg and growth parameters were within the normal range. She was born hydropic, pale, with generalized petechiae and respiratory distress. She had been resuscitated aggressively including blood transfusion.

Her initial lab results were as follows; hemoglobin level 4.1 g/dl, reticulocytes 10-14%, platelet 8000/ml, white blood cells 20,100/ml and no coagulation abnormalities were evident. Liver function tests were normal except for the low level of albumin 1.4 g/dl. Direct bilirubin was 0.6 mg/dl, but rapidly increased to 22.6 mg/dl by the tenth day with normal liver enzymes. Hemoglobin electrophoresis showed hemoglobin A 89.5%, hemoglobin A2 2.6%, and hemoglobin F 7.9% interpreted as a normal hemoglobin fractionation pattern after transfusions. Coombs' test showed 2 positive results, however, insignificant after transfusions. Labs also revealed negative DCT and Ham test. Evaluation for neonatal lupus revealed negative results. Antiphospholipid antibody panel, Alpha 1-antitrypsin, immunoglobulins were all normal. All viral serology was negative. Follow-up investigations of Brucella IgM and IgG, syphilis and malaria were negative. Metabolic screen and chromosomal analysis were normal. As for imaging investigations, the chest x-ray and echocardiogram showed bilateral pleural effusion

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with minimal pericardial effusion which resolved spontaneously. Ultrasonography showed ascites and hepatosplenomegaly without any gallbladder or biliary ductal abnormalities. The brain CT showed no intracranial bleeding. The bone marrow aspiration showed active and normal bone marrow. During her initial stay, serum ferritin was requested, and it came markedly elevated (3000 ng/ml), which is not explained merely by a couple of blood transfusions that she received. Total iron binding capacity was 23 and transferrin was 1. A liver biopsy could not be obtained because of the instability of the patient's condition and the parents' refusal. The hemochromatosis gene was requested, and it came positive for H63D gene mutation. Since then, she was maintained on packed RBCs and platelet transfusions, iron chelating agents, and IV immunoglobulins to manage the query of both HH as well as NH. This patient stayed for few months and eventually went into a stage of acute liver failure. She was put on the list for a liver transplant but was deceased before getting the chance for transplantation.

DISCUSSION

Many mutations of at least five genes, encoding proteins to regulate serum iron, were implicated to be causing HH. These include; HFE, TfR2, HJV, SLC40A1, and HAMP [(2)]. HFE gene, being the most commonly inherited mutation, is located on the short arm of chromosome 6. Expression of a defected HFE protein on enterocytes leads to upregulated absorption of iron [(8)]. The first attributed mutation C282Y. Its worldwide frequency is about 1.9%, the homozygosity is in approximately 0.26% of cases. The second mutation is H63D. It represents 8.1% of the cases, 1.89% are homozygous. Compound heterozygosity of the former mutations is estimated to be 1.97% [(1,6)].

Vague nature of early-disease symptoms and variable penetrance of the mutations can attribute to underdiagnosis of HH. Studies have found that homozygosity of C282Y is considered the most penetrant [(1,4)]. Heterozygosity with H63D, as well, increases the risk of HH [(6)]. Many studies have failed to exactly identify the H63D role in the disease development or progression, despite its homozygosity. Researchers have reported a low or variable penetrance that can merely cause an elevation in iron indexes [(5)], including a meta-analysis which concluded that C282Y homozygosity was 100 times more strongly associated with iron overload than H63D homozygosity [(1,6)]. Other studies contradict that and prove H63D causing the disease in the presence of other factors or mutations i.e. environmental factors or mutated genetic modifiers [(1,6,7)]. This may help to explain the variability of penetrance of HH generally, and H63D in specific, in some patients whom their homozygous H63D progressed to overload.

Both HH and NH manifest as hepatic and extra-hepatic siderosis, signs of liver and organ failure with severe coagulopathy, in addition to laboratory investigations showing iron overload, including hyperferritinemia.

The neonatal type is characterized by neonatal death or liver disease with high rates of recurrence in pregnancies. It is also characterized by early intrauterine changes such as growth retardation, oligohydramnios, placental edema, and sometimes polyhydramnios. Moreover, the pregnancy frequently ends with stillborn infants, prematurity, or small for gestational age. Diagnosis of NH is done by exclusion of other causes of liver failure. Other diagnostic procedures are not always feasible in the severely ill newborns and the diagnostic accuracy of such methods have not been studied appropriately in neonates. Experience with the treatment in the past included postnatal treatment of NH with anti-oxidants and chelation therapy.

Survival rates associated with this therapeutic regimen are lower than 20% for which recent studies suggested replacement or addition of this approach to exchange transfusions and IVIG administration with survival rate reaching up to 79% [(9)].

On the other hand, there are other genetic disorders of hyperferritinemia in neonates which include hemophagocytic lymphohistiocytosis (HLH). The clinical and laboratory diagnostic criteria for HLH outlined by the familial hemophagocytic lymphohistiocytosis (FHL) Study Group of the Histiocyte Society included fever and the documentation of hemophagocytosis in bone marrow plus an association with herpes simplex virus was found in many of the cases. Hereditary hyperferritinemia-cataract syndrome (HHCS) is an autosomal dominant disease, that is also associated with hyperferritinemia but with the absence of iron overload. Aceruloplasminemia, which is characterized by hyperferritinemia and the development of iron overload, however, neurological symptoms are commonly present. Other excluded causes of hyperferritinemia acting as a pro-inflammatory mediator include septic shock and inflammation.

In our case, the diagnosis remained inconclusive. The increased penetrance was assumingly postulated after taking a detailed family history of iron overload and it was found that a first-degree family member is being treated

for high iron levels with the traditional treatment of HH including phlebotomy and oral chelating agents. The frequency of H63D homozygous genotype was found to be influenced by non-genetic modifiers [5], as well as by what we have explained earlier regarding how variable penetrance can be affected in such cases [1,6,8].

That in addition to the possibility of NH meanwhile, regardless of the absence of all characteristics in relation to our case and failure of all therapeutic measurements postnatally.

CONCLUSION

The presence of a homozygous p.H63D genotype in HFE in the baby might be a casual association due to the high prevalence of the variant in the population and cannot be implicated as the cause of the very high serum ferritin level and even less in the supposed severe iron overload.

We assume, from our clinical background and the literature review, that the increased penetrance might have been caused by other mutations of HH of more sever forms or other coexistent HFE mutation not have been screened, or mutations not yet known to cause iron overload. Our second assumption is the presence of strong environmental factors.

NH on top of HH might have played a role in the progression to liver failure despite all therapeutic measurements. It is of foremost importance to try to identify factors associated with increased penetrance of H63D gene mutation or others, i.e. NH, as this will raise our awareness and would enable us to distinguish when to expect cases in early ages from those which will remain asymptomatic.

CONFLICT OF INTERST

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript for publication.

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